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STREPTOMYCIN FOR PENICILLIN-RESISTANT SUBACUTE BACTERIAL ENDOCARDITIS

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Section on Cardiovascular Disease

ALTHOUGH penicillin is the drug of choice for the treatment of subacute bacterial endocarditis due to nonhemolytic streptococci, there is a group of cases in which the antibiotic agent fails to arrest the infection. In some of these cases the organism is resistant to penicillin from the beginning, while in others resistance apparently is acquired during the course of therapy. Treatment, in the former instances, does not affect the fever or the clinical course of the illness, but in cases belonging to the latter group, the evidence of infection is temporarily controlled, only to relapse while the drug is still being administered or shortly after it has been discontinued. Hunter[1] has recommended that streptomycin be employed in the treatment of these penicillin-resistant cases, and the present report summarizes two instances in which therapy of this kind successfully controlled the infection.

Case Reports

Case 1. A white man, aged 42, had had several teeth removed two and one-half months before his first visit to the Clinic. Approximately twelve hours after the extractions he experienced a severe chill followed by fever. Six weeks later, because of increasing weakness and fatigue, persistent afternoon fever, and frequent night sweats, he was admitted to a hospital. A blood culture yielded a growth of Streptococcus viridans, and an unknown amount of penicillin was administered by intramuscular injection every three hours for three and one-half days. He was then discharged, but the fever and other symptoms returned within two or three days. Three weeks later he was admitted to the Clinic. There was a history of rheumatic fever in childhood.

On physical examination, the temperature was 100.4 F., the pulse rate 120, and the blood pressure 108 systolic, 68 diastolic. The heart was not enlarged, and its rhythm was regular. A moderate systolic murmur was present at the apex. The spleen was readily palpable. There were no petechiae. The blood culture was positive for Str. viridans.

Penicillin was administered in doses of 25,000 units every two hours by intramuscular injection. The temperature returned to normal within twenty-four hours and did not rise above normal during the remaining seven days of hospitalization. Penicillin was continued at home in the same amounts for the next two weeks, but at the end of that time the temperature again became elevated and the patient therefore was readmitted to the hospital. The blood culture was positive for Str. viridans. The dosage of penicillin was increased to 50,000 units every two hours. The temperature returned to normal on the fourth day, but when treatment was terminated at the end of six weeks, fever reappeared almost immediately, and the patient experienced several mild chills. A blood culture made three days after the last injection of penicillin again yielded a growth of Str. viridans. Penicillin was resumed in doses of 50,000 units every two hours, and intramuscular injections of streptomycin also were given in doses of 0.5 Gm. every three hours until a total of 20 Gm. had been administered. The fever was promptly controlled. Penicillin was continued for three and one-half weeks. It is now fourteen months since treatment was completed, and during this time there has

been no evidence of relapse. Periodic blood cultures have been uniformly negative, and for several months the patient has been doing light work.

Case 2. A white woman, aged 45, had had daily low-grade fever for one year before coming to the Clinic and had noted gradually increasing general malaise, fatigue, weakness, and dyspnea on exertion. For many months she had received penicillin by intramuscular injection in amounts sufficient to give a daily total of 500,000 units to 1,000,000 units. Approximately 200,000,000 units of penicillin had been administered during this time, but the fever and other symptoms had not been noticeably affected. There was a history of growing pains in childhood.

At the time of admission, the temperature was 103.2 F., the pulse rate 120 per minute, and the blood pressure 134 systolic, 40 diastolic. The skin and mucous membranes were pale, a "splinter hemorrhage" was present beneath the nail of the left third finger, and there was a small petechia in the conjunctiva of the left lower eyelid. The heart was moderately enlarged, and its rhythm was regular. A short systolic murmur was present at the aortic area, and the aortic second sound was followed by a prolonged, low-pitched diastolic murmur which was transmitted downward along the left border of the sternum. A soft systolic murmur was present at the apex. The left ankle was swollen and moderately tender. Blood cultures were positive for Str. viridans.

Penicillin by intramuscular injection in doses of 50,000 units every two hours had no effect upon the fever, and at the end of five days the dose was increased to 100,000 units every two hours. The temperature remained elevated, and at the end of twelve days' treatment the blood culture was still positive for Str. viridans. Penicillin therapy was continued, but the patient was also placed upon streptomycin in doses of 0.5 Gm. by intramuscular injection every three hours. The temperature returned to normal within forty-eight hours, but on the following day fever again developed and was accompanied by a generalized macular rash, pharyngitis, and vertigo. Streptomycin was continued until a total of 30 Gm. had been administered. The temperature remained elevated throughout this period, reaching a maximum of 104 F. on the sixth day, but returned to normal within twenty-four hours after the last dose and remained normal during the remaining four weeks of hospitalization. Penicillin was continued until the day of discharge. There has been no recurrence of symptoms, and the patient is in satisfactory health one year after leaving the hospital.

Discussion

The 2 cases which have been presented demonstrate that under certain circumstances streptomycin may be of life-saving importance in the treatment of subacute bacterial endocarditis. Because of the frequency with which its use in large amounts results in symptoms of toxicity, the drug, however, is not to be preferred to penicillin in the management of the usual case of this condition. Penicillin in adequate amounts can be expected to result in the cure of at least 75 per cent of all cases of nonhemolytic streptococcus endocarditis, and because the incidence of undesirable reactions to this antibiotic agent is so remarkably low, it is the preparation of choice. It is believed that streptomycin should be used only in those cases in which penicillin fails to control the infection. The recent introduction of caronamide as an agent for enhancing penicillin serum concentrations[2,3] offers a promising prospect of considerably reducing the number of cases of subacute bacterial endocarditis in which penicillin therapy is unsuccessful. As a result the role of streptomycin in the treatment of this condition probably will be limited further, but occasional cases in which the use of the drug will be indicated undoubtedly will still occur.

Measurements of the penicillin sensitivity of the infecting organism are desirable in all cases of subacute bacterial endocarditis, but the results of such

measurements cannot be taken as an infallible guide to treatment and prognosis.[4] In the first of the cases reported in the present communication, growth of the organism was inhibited by penicillin in a concentration of 0.03 units per cc., while in the second, 0.25 units per cc. were required. These findings suggest that larger amounts of penicillin might have been effective, although theoretically the dosage employed in the latter part of the treatment of the first patient should have been sufficient.

Since these patients were treated it has become our practice to administer penicillin by continuous intramuscular drip rather than by intermittent intramuscular injection and to begin treatment with a dose of 1,000,000 units a day. As soon as the penicillin sensitivity of the infecting organism has been determined, the daily amount of the drug is adjusted up or down to the smallest amount that will maintain a serum level approximately four times as high as the amount required to inhibit the growth of the organism *in vitro*. Dawson and Hunter[5] have recommended this level and have published a table which can be used as a guide to the dose of penicillin necessary to obtain the desired serum concentration when continuous intramuscular administration is employed. This method is very satisfactory when the indicated daily dose is 2,000,000 units or less, but for larger amounts continuous intravenous drip is to be preferred. Treatment is continued for three weeks, and the patient is then kept under close observation for several weeks for evidence of relapse.

In the cases presented, penicillin was continued during the time streptomycin was being administered. Whether the successful results were due to the combined use of the two preparations or are to be attributed to streptomycin alone cannot be stated. Hunter,[1] however, has pointed out certain considerations which might make combined antibiotic therapy more effective than the use of either penicillin or streptomycin alone.

Summary

Two cases of subacute bacterial endocarditis due to Str. viridans are reported in which penicillin failed to control the infection but recovery resulted when streptomycin was added to the treatment.

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CHONDROMA OF THE LARYNX

Report of a Case

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THE rarity of chondromata of the larynx is attested by the relatively small number of cases which have been reported. The first comprehensive survey of the world's literature was made by Irwin Moore[1] in 1925. He collected 53 cases which he considered true cartilaginous tumors. The most recent survey (1944) was made by McCall, Dupertuis, and Gardiner,[2] who collected an additional 30 cases since Moore's report. They have summarized each case and have added 2 of their own, making a total of 85 cases. A case reported by Rosedale[3] and the one herewith reported bring the total to 87 cases.

The most frequent site of development of chondroma of the larynx is the endolaryngeal surface of the posterior plate of the cricoid cartilage. The next is the thyroid cartilage, then the epiglottis and the arytenoid cartilage. In Rosedale's case the chondroma arose from the cricoid cartilage, while in ours the tumor had its origin in the left ala of the thyroid cartilage.

Hoarseness and dyspnea are the commonest symptoms, and cough or dysphagia may develop. There may be an external deformity in the neck when the chondroma arises from the thyroid cartilage. The symptoms are caused by obstruction of the airway and interference with the function of the larynx, and they depend upon the location and size of the tumor. Since these tumors usually grow slowly the symptoms increase so gradually that the chondroma may be very large before the patient seeks relief.

The chondroma is usually smooth, rounded, hard, non-compressible, and is covered by a normal or thinned mucous membrane in which the blood-vessels are often prominent. It is firmly attached to the cartilaginous box of the larynx.

The only treatment for this condition is surgical removal of the tumor, the method depending upon its size and location. Direct laryngoscopy and endolaryngeal removal is successful when the tumor is small and accessible, but as the chondroma becomes larger more extensive procedures are required. When it is attached to the cricoid cartilage, laryngofissure with complete removal of the growth is the method of choice. If it arises from the thyroid cartilage it may be removed by an external approach and submucous resection or morcellation without incising or removing any of the laryngeal mucosa. It is necessary to remove every fragrant of the tumor with a fairly wide margin of the thyroid cartilage around its attachment in order to avoid recurrence. This method was employed by New[4] in a case reported in 1918, Waggett[5] in 1921 and again in 1925,[6] Neilson[7] in 1929, Figi[8] in 1932, Holinger and Matzkin[9] in 1942, and in the case reported in this paper. In Waggett's case there was

a recurrence in three years, and a more extensive removal with laryngeal mucosa was performed. In Figi's patient the chondroma recurred six years later, at which time a laryngectomy was advised and refused. All of the procedures mentioned leave a normally functioning larynx. A total laryngectomy is required when the chondroma has attained such size that its removal entails a sacrifice of a sufficient amount of the framework of the larynx to result in a collapse and stenosis. Laryngectomy has been done in 14 of the reported cases, including the 2 by McCall *et al.* and the 1 by Rosedale.

Case Report

A white man, aged 60, came to the Cleveland Clinic on March 1, 1939. He stated that he had enjoyed excellent health until two years ago. At this time he noted a small growth in the left side of the neck just lateral to the Adam's apple. This had gradually increased in size. A slowly progressive hoarseness had developed and was constantly present, having become especially pronounced during the past two months. He had had a chronic non-productive cough and some dyspnea for the past three months. The dyspnea had increased so that some was present even while he was at rest. There had been no pain in the neck and no dysphagia or odynphagia. There had been no loss of weight or appetite.

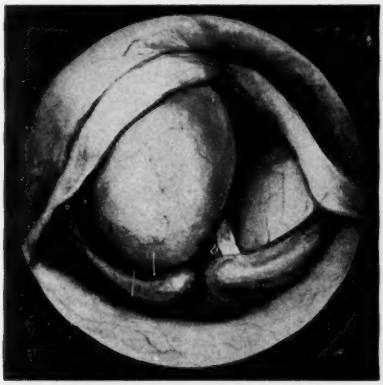

FIG. 1. View of larynx through laryngoscope.

The general physical examination revealed a muscular well developed man with a blood pressure of 165 systolic, 90 diastolic. There were no abnormal observations other than the tumor in the neck, which was the size of a large olive and was firmly attached to the left ala of the thyroid cartilage. It was of hard consistency and was not tender to palpation. The mass moved with the larynx during the act of swallowing and of speaking. The skin was freely movable over the tumor and appeared normal. There was no palpable cervical adenopathy.

The sinuses were clear to transillumination. The nasal passages showed no abnormalities. There were only a few lower teeth remaining, and these showed signs of oral neglect. The tonsils were of moderate size. The ears contained some moist debris.

Mirror laryngoscopy revealed a marked distortion of the larynx. There was a large, smooth, rounded tumor mass above the glottis and in the region of the left aryepiglottic fold. This mass was so large that neither vocal cord could be visualized. The opening into the larynx was displaced to the right and the airway appeared restricted. The mucous membrane overlying the tumor mass was smooth and normal in appearance. On direct laryngoscopy (fig. 1)

the tumor was found to be hard and firmly attached to the laryngeal box. It could not be compressed or displaced to obtain a view of the cords. No biopsy was taken from the interior of the larynx.

Roentgenologic examination of the chest was negative. A lateral roentgenogram of the larynx (fig. 2) showed a large tumor with calcified walls.

A tentative diagnosis of chondroma of the larynx arising from the left ala of the thyroid cartilage was made.

The patient was admitted to the hospital on March 6, 1939, and the teeth were cleaned and the gums treated prophylactically in the Department of Dentistry. On March 7 a tracheotomy and surgical removal of the chondroma was performed. The tracheotomy was done because of the patient's dyspnea and the possibility that the surgical removal might temporarily increase the obstruction. Nembutal, morphine, and atropine were administered as preoperative analgesia. Two per cent pontocaine was applied to the oropharynx, pyriform sinuses, epiglottis, and larynx. One-half per cent novocain was injected regionally into the neck. An orderly low tracheotomy was performed first. A second incision was then made horizontally over the tumor mass in the left side of the neck. This incision was about 2½ inches

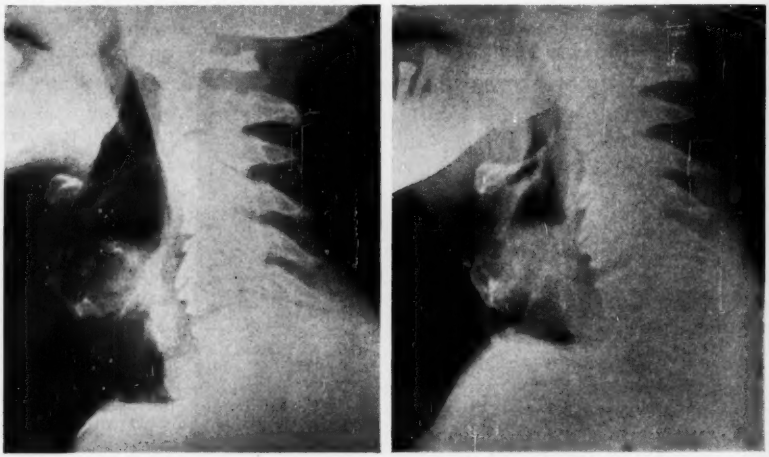

FIG. 2. Lateral roentgenograms of neck showing tumor mass in larynx.

long and extended to within ½ inch of the midline. The soft tissues were separated down to the tumor and the thyroid cartilage. A window was cut through the thyroid cartilage around the periphery of the external portion of the chondroma. The internal portion of the mass was removed by morcellation, using a large mastoid curette. This procedure was continued until every visible vestige of tumor had been removed from the mucous membrane of the interior of the larynx. The mucous membrane was not torn or incised. A small vaseline drain was inserted into the cavity, and the incisions were closed with buried catgut sutures in the fascia and muscle and with clips in the skin.

The tissue was examined by Dr. Allen Graham. The fragmented tumor mass weighed 20 Gm., and all of the pieces had similar gross characteristics suggestive of cartilaginous tissue with relatively no ossified tissue or gross bone. The microscopic examination showed well differentiated hyaline cartilage with no definite bone present and no histologic evidence of malignant disease.

The postoperative course was uneventful. A cork was placed in the tracheotomy tube on the third postoperative day, and the tube was removed on the sixth postoperative day.

The patient was discharged from the hospital on the eighth postoperative day. On March 27, 1939, the operative wounds were entirely healed, and he was told to return in one month for observation.

He returned on August 24, 1943, complaining that for the past six months he had experienced trouble breathing when he walked rapidly and climbed stairs. He had noticed an external lump in the neck for the past year. Examination showed a recurrence of the chondroma of the larynx, causing some external deformity over the left wing of the thyroid cartilage. Laryngoscopy revealed a larger internal mass displacing the left side of the larynx across the midline and narrowing the glottis to a small chink. The left cord appeared fixed. Lateral roentgenograms of the neck again showed a large tumor mass involving the larynx, estimated to be about 4 cm. in diameter. The advisability of doing a total laryngectomy was discussed with the patient and his family, but since he was now 64 years old and the previous operation had given him four and one-half years of comfort, it was decided to remove the tumor again by morcellation. He was admitted to the hospital on September 8, 1943. On September 9 a tracheotomy was again performed and the chondroma removed by morcellation under local anesthesia combined with sodium pentothal. Almost all of the left wing of the thyroid cartilage was removed at this time. On the sixth postoperative day the tracheotomy tube was closed with a cork, and the tube itself was removed on the eighth postoperative day. He was discharged on the tenth postoperative day. He returned faithfully until the tracheotomy wound was completely healed but did not come in for follow-up observation.

On August 24, 1946, he returned with a third recurrence of the chondroma. This time it was only a small, hard, freely movable mass attached to the skin at the level of the thyroid cartilage on the left side of the neck. There was no encroachment on the interior of the larynx. The vocal cords were normal in appearance and in movement, and the voice was of excellent quality. Since this recurrent mass was small, not attached to the larynx, and just beneath the skin, he was not admitted to the hospital. The mass including the skin to which it was attached was removed by dissection under local anesthesia, and he was allowed to return home.

The specimen consisted of tissue from the left cervical region. On gross examination there was an elliptical portion of skin 3.2 x 1.2 cm. with hair stubble and several clamp marks incident to the surgical procedure. Beneath the skin was an ovoid mass 2 x 1.8 x 1.6 cm., the external surface of which was nodular. It was firm and semi-elastic, pale gray, and semi-translucent. A small amount of fatty tissue was attached to the surface.

It cut with resistance and presented a cystic center 1.5 cm. in greatest diameter, filled with a thick, mucoid, colorless liquid. The wall was 0.3 cm. in thickness, white, homogeneous, hard, and scraped with a grating sensation. It had the appearance of cartilage.

Upon microscopic examination the nodule was comprised of hyaline cartilage with nuclei irregularly clumped but fairly well lacunated. There was some variation in nuclear size, but no mitoses were found. There was an irregular bluish staining zone free from nuclei in the center. A thin zone of fibrous tissue surrounded the nodule, growing in the corium and apparently not in the subcutaneous layer.

Summary

A chondroma of the larynx in a man 60 years old is reported. This rose from the left ala of the thyroid cartilage, presenting a large obstructing mass within the laryngeal box and a smaller external extension into the neck. The tumor was removed in 1939 by morcellation, using an external approach. A portion of the thyroid cartilage was removed from around the point of attachment. The interior of the larynx was not entered. The patient returned with a recurrence four and one-half years later, at which time the tumor was almost as large as the original one and was again causing signs of laryngeal obstruction. The same method of removal was used, but, in addition, the left ala of the thyroid cartilage was removed. There was a third recurrence three years later, but the mass was quite small and was attached to the skin but not to the

larynx. Malignant changes did not develop in this growth. During the seven years that the patient was under observation and treatment he had had normal function of the larynx except for relatively short periods before and after operation. The first recurrence may have been the result of removing too small an amount of thyroid cartilage from around the attachment of the chondroma.

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GIANT URETHRAL CALCULUS

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THE occurrence of calculi within the male urethra is uncommon. LeComte[1] encountered this condition seven times in a series of 2900 urologic cases. Debenham[2] reported 40 cases of urethral calculi admitted to the London Hospital from 1910 to 1930, 3 patients being women and 37 men. Kini[3] found only 1 case of calculi among 102 patients with stricture of the male urethra.

Urethral calculi are classified as primary or autochthonous and secondary or migratory calculi, depending on their site of origin. Autochthonous calculi occur more rarely and are usually formed in the urethra behind some obstruction or diverticulum. Secondary calculi are formed in other parts of the urinary tract and migrate to the urethra. Differentiation between autochthonous and secondary calculi may be difficult. According to Culver,[4] Legueu believed that every urethral calculus originated in the kidney or bladder and became urethral secondarily. Stevens[5] admits that autochthonous calculi are less common than secondary calculi and that their formation depends upon certain abnormal local conditions such as stricture, congenital or acquired dilations, diverticula, and prostatic hypertrophy. The recent work of Wilson, Benjamin, and Leahy[6] demonstrating the production of urethral calculi in newborn rats by injection of estradiol raises the question of endocrine influence upon urethral calculi.

Most authors agree that migratory stones have a nucleus of uric acid or calcium oxalate, while autochthonous stones are phosphatic in composition and uniform in structure, being formed in infected urine.[7,8,9]

Case Report

A man, aged 66, was admitted to the Cleveland Clinic on August 11, 1947, complaining of frequency of urination for one year. Past history revealed that in 1911 he had fallen from a crane into some steel castings and had sustained a fractured pelvis with rupture of the urethra. He was treated with a suprapubic cystotomy and an indwelling urethral catheter. No postoperative treatment was instituted, and in 1915 he had developed a urethral stricture, had had a perineal urethrotomy, which was followed by formation of stricture, and a second perineal urethrotomy in 1930. Since July, 1946, he had had hourly frequency of urination. The family physician had been unable to introduce a catheter into the bladder and had made a diagnosis of carcinoma of the prostate.

Physical examination revealed a well developed and fairly well nourished obese white man, 69 inches in height and weighing 198 pounds. He walked with a limp to the right. The chest and heart were normal, and the blood pressure was 130 systolic, 80 diastolic. On abdominal examination a mass was palpated from the symphysis pubis to just below the umbilicus. Anterior to the mass a well-healed scar was present. The left testicle was absent. Rectal examination revealed a few external thrombotic hemorrhoids. There was a grade II enlargement of the prostate which seemed to be stony hard, fixed, and nodular, yet slightly tender to palpation. Multiple scars were present in the midperineum.

A filiform was introduced into the bladder but a number 8 follower could not be admitted because of obstruction in the prostatic area.

Examination of the urine showed a specific gravity of 1.012, alkaline reaction, a trace of albumin but no sugar. Microscopic examination demonstrated numerous red and white

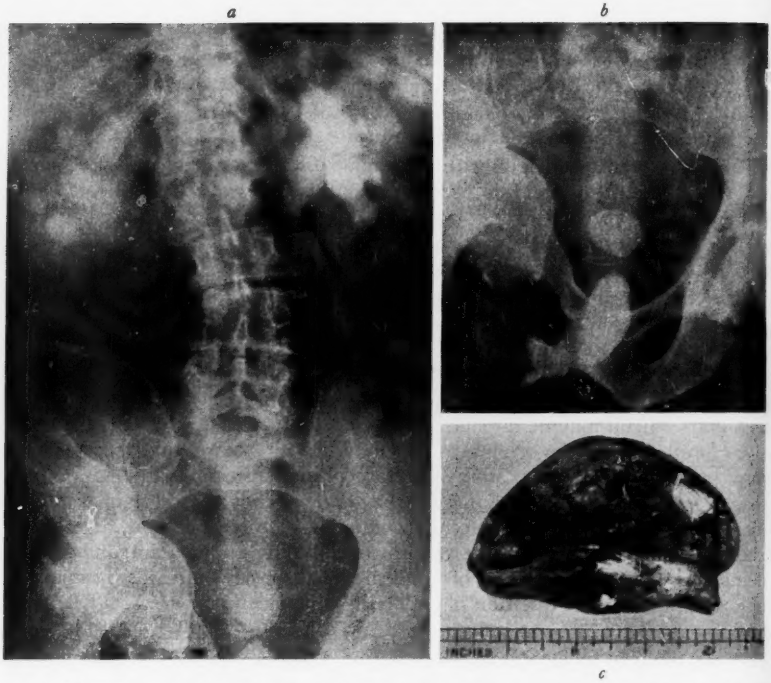

FIG. 1. (a) Bilateral hydronephrosis with calculus in bladder and urethra; (b) Calculus in bladder and large calculus in urethra; (c) Photograph of urethral calculus.

blood cells per high power field. Bacillus coli and Streptococcus faecalis were cultured from the urine. The blood count disclosed 4,720,000 red cells, 6050 white cells, and 12.5 Gm. of hemoglobin. Blood urea was 42 and sugar 110 mg. per cent three hours postprandially. The Wassermann and Kahn reactions were negative. Acid phosphatase was .8, and alkaline phosphatase was 1.8 Bodansky units.

Roentgenologic examination of the kidneys, ureters, and bladder showed no disease process in the kidneys or ureters. There were pronounced hypertrophic arthritic changes throughout the lumbar region of the spine and partial protrusion of the right femoral head into the pelvis. There was evidence of an old healed fracture of the right pelvic bone. A large calculus was present in the bladder and a second large calcification overlying the symphysis, partially in the bladder or urethra, was seen (fig. 1 a & b). An intravenous pyelogram showed prompt function from both kidneys, but both kidneys were hydronephrotic. The left ureter was dilated throughout its entire course.

The patient was admitted to the hospital, and on August 18, 1947, an internal urethrotomy was performed, severing strictures from the bulbous urethra to the meatus. Convalescence was uneventful, and on August 20, 1947, a suprapubic cystolithotomy was performed. After the bladder was opened and the calculus removed the internal meatus was dilated. A calculus was then palpated in the urethra. The anterior aspect of the vesical neck was incised, and a large calculus lying in the prostatic bed was extracted (fig. 1c). A number 18 soft rubber catheter was then easily introduced into the bladder. Convalescence was uneventful, and the patient was discharged from the hospital on September 10, 1947. At the

time of discharge he was voiding normally, but some pyuria was still present. Rectal examination revealed a grade I enlargement of the prostate. The stony hard area had disappeared.

Upon laboratory analysis of the calculus the specimen consisted of one tan and brown stone measuring 5 x 3 x 2.5 cm. The surface was smooth, the contour irregular. The interior was cream colored and striated, showing several darker tan striations. It was positive for nitrogen, ammonium, and phosphates.

Comment

Although the patient was referred to the Clinic with a diagnosis of carcinoma of the prostate, this error in diagnosis was understandable. Because of the anterior urethral strictures, no instrument could be passed into the bladder and the diagnostic "metal click" could not be elicited with the filiform. Rectal examination was not diagnostic, as the mass was not movable and no crepitus could be elicited. The history of trauma, previous perineal surgery, normal acid and alkaline phosphatase units, and positive roentgenologic findings led to the presumptive diagnosis of urethral calculus, which was confirmed at operation.

From reports of similar cases in the literature, it is apparent that trauma to the urethra followed by stricture formation is a salient point in the etiology of posterior urethral calculi. This is exemplified by case reports of Bertin,[10] Miller,[11] and others.[12,13]

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THROMBOANGIITIS OBLITERANS

A Summary of Recent Trends and Treatment

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DURING the past three or four years several new methods for the treatment of thromboangiitis obliterans have been suggested. The most promising have been the anticoagulants, histidine and vitamin C, sympathectomy, tetraethyl ammonium chloride, and caudal anesthesia or lumbar sympathetic block. These, however, should be considered only as supplements to the well-established principles and methods used in the management of thromboangiitis obliterans, namely, elimination of tobacco, careful hygiene and care of the extremities, and proper physical therapy measures.

Anticoagulants

Following the introduction of heparin and dicumarol as anticoagulants to be employed in the treatment of thromboembolic disease, it was suggested that these preparations might be helpful in thromboangiitis obliterans. Comparatively little coordinated or extensive work has appeared in the literature concerning such use for these anticoagulants. In 1942 Allen *et al.*[1] reported the use of dicumarol in 2 cases, but significant conclusions as to its value could not be drawn. LeFevre[2] employed the same substance in 8 cases in 1945 but, noting no definite changes, believed that dicumarol had little effect upon the course of the disease. In 1946 Aggeler[3] reported that the anticoagulants had been given in chronic occlusive arterial disease but that their benefits had not yet been determined. Barker[4] in 1945 stated that dicumarol was beneficial after acute peripheral arterial thrombosis from any cause and that possibly it might prevent an extending arterial thrombosis such as that present in thromboangiitis obliterans. In 1946 Barker *et al.*[5] reported the treatment of acute arterial occlusion of the e tremities with special reference to anticoagulant therapy. Three cases of thromboangiitis obliterans were recorded in which both heparin and dicumarol were employed. Recovery of the limb ensued in each case, indicating that progressive thrombosis and gangrene do not develop while anticoagulant therapy is being given. In 1944 Gefter[6] treated 2 cases of thromboangiitis obliterans with dicumarol and noted partial improvement. In 1947 Allen[7] summarized the present status of the anticoagulants in the chronic occlusive arterial diseases by stating that the results have not been satisfactory.

Method of Treatment. The administration of heparin and dicumarol depends upon the acuteness of the disease state. In the acute thrombotic processes, heparin and dicumarol therapy should be started simultaneously. Fifty milligrams of heparin solution is drawn into a syringe containing about

15 to 20 cc. of a physiologic saline solution and given intravenously every four hours for ten doses. On the first day the prothrombin time is recorded and the patient is given 300 mg. of dicumarol orally. One hundred and fifty milligrams of dicumarol is again given on the second day. Following this the dosage of dicumarol is adjusted to keep the prothrombin time between 20 and 30 per cent of normal. We have found this to vary with each patient. The prothrombin time should be observed daily. Caution should be used to take the prothrombin time at least three hours after heparin has been given, as it has been shown that heparin will affect the prothrombin time. In the chronic occlusive states, the heparin can be omitted.

Comment. Although the exact role that heparin and dicumarol will play in the treatment of thromboangiitis obliterans has not yet been determined, conservative evaluation indicates that the anticoagulants should be employed in acute cases. The occurrence of venous thromboses and rapidly progressive arterial thromboses, such as in acute thromboangiitis obliterans, appears amenable to the action of the anticoagulants. In the chronic forms of Buerger's disease where there is no active thrombotic process the administration of anticoagulants hardly seems justified.

Histidine and Vitamin C

Considerable interest has been centered about the treatment of occlusive vascular disease with histidine and vitamin C. As in all these newer methods, the primary aim is to increase the supply of blood to the affected extremity. Up to the present time only one reference to treatment with these materials has appeared in the literature.[8] Two cases of thromboangiitis obliterans were treated by histidine and vitamin C, and the observers noted a rapid response with relief of pain, a sensation of warmth, and an increase in temperature of the affected extremities.

Egeberg[9] used histidine and ascorbic acid in 50 patients, 11 of whom had thromboangiitis obliterans. Three of the 11 had osteomyelitis and underwent amputation. Three cases were mild and showed improvement; 5 were severe and were improved by these substances. Egeberg believes that two to three months of continuous therapy may be necessary before favorable results are apparent.

Technic. The patient is given 500 mg. of sodium ascorbate. This is followed immediately by the intramuscular injection of 5 cc. of a 4 per cent aqueous solution of histidine monohydrochloride and the simultaneous injection of 100 mg. of sodium ascorbate subcutaneously. Care is taken to inject these substances in different locations. This treatment is given every four hours. In addition, 600 mg. of ascorbic acid is given by mouth daily. Results should be evident within a few days. The length of therapy has not been established, although Egeberg believes two to three months should be the average duration of therapy.

Comment. In 2 typical cases of thromboangiitis obliterans treated at the Clinic in this manner for ten days improvement could not be established.

Despite this, we believe that further work along this line is justified, considering Egeberg's views regarding the length of time necessary for a favorable response.

Tetraethyl Ammonium Chloride

Tetraethyl ammonium chloride has been shown to block the autonomic ganglia. Because of this effect it was believed that this substance might be beneficial in relieving the neurogenic vasoconstriction which is frequently present in thromboangiitis obliterans.

In 1946 Berry *et al.*[10] reported the treatment of 18 cases of thromboangiitis obliterans with tetraethyl ammonium chloride. Of 11 which were treated conservatively over a period of two weeks to six months, 5 became symptom-free. Intermittent claudication was relieved, and the exercise tolerance improved in all members of the group. A sympathectomy was performed on 3 of these patients. Three of the patients received only single injections for the purpose of producing a sympathetic block.

In 1947 Lyons *et al.*[11] reported the effects of blockade of the autonomic ganglia by tetraethyl ammonium in man. This report included cases of thromboangiitis obliterans, and it was concluded that patients with Buerger's disease experienced continued relief of pain and a decrease in the inflammatory process. Lyons' group also felt that the use of tetraethyl ammonium chloride was a diagnostic agent helpful in evaluating neurogenic vasoconstriction and therefore of aid in determining the importance of lumbar sympathectomy in cases of thromboangiitis obliterans. This preparation was believed to be as reliable as paravertebral blocks or local nerve blocks.

Technic. All of the material we have used was supplied through the courtesy of Parke Davis and Company. The material is furnished as a powder which is dissolved in highly distilled water so that each cubic centimeter of solution contains 100 mg. This preparation can be given either intravenously or intramuscularly, although with this concentration we used only the intramuscular route. We used an average daily dosage of 3 cc. intramuscularly for three to six weeks. The intravenous route should be used more cautiously and the solution given very slowly, as the blood pressure may drop precipitously. With both modes the blood pressure should be watched for at least forty-five minutes.

Comment. We have treated 4 patients with thromboangiitis obliterans in this manner. One was an acute case and did not show significant improvement following therapy. Three chronic cases of thromboangiitis obliterans were treated over a period of three months with evidence of increase in the peripheral circulation and relief of symptoms. We have concluded that tetraethyl ammonium is a promising drug in treatment of thromboangiitis obliterans. Too few cases have been reported for final evaluation. Further investigation is indicated.

Sympathectomy

Sympathectomy has been recognized for several years as a procedure of importance, and more recently it has been possible to draw conclusions con-

cerning the success of this operation. Recent reports in the literature continue to stress its importance. In 1944 DeTakats[12] discussed the value of sympathectomy in the treatment of Buerger's disease in 50 patients. Thirty-seven were able to resume full-time work, 7 returned to part-time work, and 6 remained invalids. It was his opinion that sympathectomy deprived the extremities of vasoconstrictor tone. He did not think that it influenced the course of Buerger's disease but felt that when the disease is in an inactive phase and when adequate preoperative tests reveal the presence of sufficient collateral vascular supply, sympathectomy would be of value. In 1943 Shumacker[13] reported the treatment of peripheral vascular disease by sympathectomy. He included 17 cases of thromboangiitis obliterans, and it was his impression that sympathectomy did not accomplish a great deal for the intermittent claudication associated with the disease. He stressed the importance of adequate preoperative selection of cases, particularly those demonstrating significant vascular spasm. In 1947 Freeman[14] observed good results following sympathectomy in 34 cases. Of his series 31 improved, although 5 required minor amputation; 3 failed to improve, 2 of these requiring amputation. Hildenbrand[15] advised that a candidate for sympathectomy should demonstrate the presence of an adequate collateral vascular bed and should be in a quiescent stage of the disease rather than in an acute one. The disease should also not show any visceral extension. Grimson[16] stated that sympathectomy may help patients with thromboangiitis obliterans, believing that such benefits may be largely related to an increase in temperature of the extremity, slight improvement of circulation, and to elimination of the constant fluctuation of tone ordinarily induced by vasomotor nerves. He believed that the lower extremities respond to sympathectomy better than the upper extremities because the legs appear to be more actively influenced by sympathetic vasomotor tone of proprioceptive origin. Sympathectomy effects its greater benefit by interrupting this vasomotor tone and also, during changes of posture, may produce an uncompensated passive vascular exercise.

In 1946, we treated 8 patients with bilateral sympathectomy. Five received definite benefit and returned to normal activities, 2 were uninfluenced, and in 1 case the disease process was apparently slowed but a minor amputation was necessary. We believe that lumbar sympathectomy is one of the most effective methods of treatment for thromboangiitis obliterans. In our experience the procedure has been of little help in the treatment of acute thromboangiitis obliterans but valuable in chronic cases and those without active inflammatory involvement, such as thrombophlebitis or ulceration.

Definite evidence of vasoconstriction should be present before operation is performed. This evidence can be demonstrated by the use of lumbar procaine hydrochloride nerve block or tetraethyl ammonium chloride.

Lumbar Sympathetic Nerve Block

Injection of procaine hydrochloride into the lumbar sympathetic nerve ganglion has been employed for several years in the treatment of peripheral vascular disease. It is helpful in thromboangiitis obliterans, particularly in

relieving associated pain. A series of nerve blocks carried out over several weeks often produces enough additional circulation to reduce the inflammation and to assist in the healing of ulcers. We recommend its use in the acute cases and as a diagnostic method for predicting the effectiveness of sympathectomy.

Caudal Anesthesia

We have recently employed caudal anesthesia as a means of relieving the exquisite pain of acute thromboangiitis obliterans. We have not found any reference in the literature to the use of this method in Buerger's disease. Caudal anesthesia has the added value of blocking not only the autonomic nerve fibers but also the sensory nerve fibers. We believe that this break in the pain cycle is very beneficial.

The procedure was first tried recently in a case in which the pain had been resistant to paravertebral block. The patient obtained his first relief with the caudal block and enabled us to proceed with further measures. In the past few months we have used the caudal block instead of the paravertebral block in all cases of occlusive peripheral vascular disease, including Buerger's disease and arteriosclerotic vascular disease. A preliminary survey reveals that in some cases this has been more effective than paravertebral block.

Summary

1. Abstinence from tobacco, careful foot hygiene, and various modes of physical therapy remain the important basic features of treatment of thromboangiitis obliterans.

2. The anticoagulants, heparin and dicumarol, appear to be of value for venous thromboses and rapidly progressive arterial thromboses. Anticoagulants do not seem to be helpful in chronic forms of Buerger's disease.

3. The evidence concerning histidine and vitamin C in thromboangiitis obliterans is inconclusive.

4. Tetraethyl ammonium chloride apparently has more value in chronic than in acute cases and may be a valuable drug.

5. Sympathetic nerve block and caudal anesthesia are helpful in relieving symptoms and in predicting the value of sympathectomy.

6. Sympathectomy helps in chronic cases of Buerger's disease but is of little use in acute cases.

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PRIMARY SPLENIC SARCOMAS OF HODGKIN'S TYPE

Review of the Literature and Report of 2 Cases

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PRIMARY malignant disease of the spleen remains a rare entity despite improvements of diagnosis and more voluminous reporting in the literature with the passing of years. Hausmann and Gaarde[1] reviewed the literature to 1940 and found a total of 178 cases, 9 of which they added from the Mayo Clinic. Twenty of these cases, however, were unconfirmed, the reports being indexed but the journals unavailable.

From 1940 to 1945, 10 more cases appear in the literature. Two of these, 1 a primary sarcoma[2] and the other a malignant hemangio-endothelioma also involving the liver,[3] are reported in unavailable journals. Garlock[4] reported an angiosarcoma; Goldberg,[5] a malignant solitary hemangioma cavernosum, a solitary macrocystic lymphangioma, and a multiple macrocystic lymphangioma; Siirala and Näätänen,[6] a primary malignant hemangioma with metastasis to the liver; Brule, Hillemand, and Isch-Wall,[7] successful splenectomy for lymphoma of the spleen with uneventful four-year follow-up; Bonney,[8] a lymphosarcoma; and Tomlinson,[9] a primary microcystic lymphangioma.

We report 2 sarcomas of the spleen from Cleveland Clinic, bringing the total of reported cases of all types of primary splenic malignant disease to 190. These 2 cases constitute the only primary malignant tumors of the spleen seen at Cleveland Clinic in two decades. In 20,000 major surgical procedures, only 1 splenectomy for primary splenic malignant disease has been performed, as indicated in the second case report.

Case Reports

Case 1. A white man, aged 50, was seen in consultation with Dr. Perry King, Alliance, Ohio, with a history of persistent generalized lower abdominal pain of ten months' duration, unrelieved at the time of its onset by a right herniorrhaphy. Surgical exploration of the gallbladder and appendix had been made four months later following x-ray examinations. Still unrelieved, the patient had been examined again by x-ray the latter part of January, 1937, at which time a lesion in the colon was suspected. He gave the history of a great deal of weight loss but no intestinal symptoms.

Examination revealed a large, firmly fixed mass in the left upper quadrant, giving the impression of carcinoma beginning in the tail of the pancreas, or possibly of hypernephroma of the left kidney. Both conditions were inoperable at this stage. The patient died on July 25, 1937, the left upper abdominal mass never having become more clearly defined than at the time the patient was first seen at the Clinic in February.

Autopsy revealed a large, indurated, nodular pancreas and surrounding lymph nodes.

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The pancreas weighed 185 Gm.; the left half was involved by a diffuse tumor growth consisting of fairly firm, white, cellular tissue which cut with considerable resistance.

The spleen was enlarged, weighing 385 Gm., and was irregular, with several large masses protruding from the outer surface. On section the tumor nodules were seen to be well localized, irregularly distributed, and varied from 2 to 5 cm. in diameter. They consisted of firm, homogeneous, white tissue with considerable stroma. The left kidney weighed 190 Gm. and measured 10 x 5.5 x 5 cm. The kidney was deformed from the pressure of the splenic tumor. Longitudinal section through the kidney showed dilatation of the pelvis and calices. No calculi nor tumor nodules were present. A portion of adrenal gland which had been compressed by the tumor was attached in the fatty tissue to the upper pole of the kidney. The prosector described no involvement of abdominal lymph nodes other than those adjacent to the nodular portion of the pancreas.

Histologic examination of the spleen showed a sarcomatous growth apparently originating in the reticular or connective tissue of the spleen. The growth was exceedingly cellular, the cells varying enormously in size, shape, and nuclear content. Many mononucleated and multinucleated giant cells were present (fig. 1). Sections from the left half of the pancreas and adjacent lymph nodes showed a tumor similar to that in the spleen. Sections from the

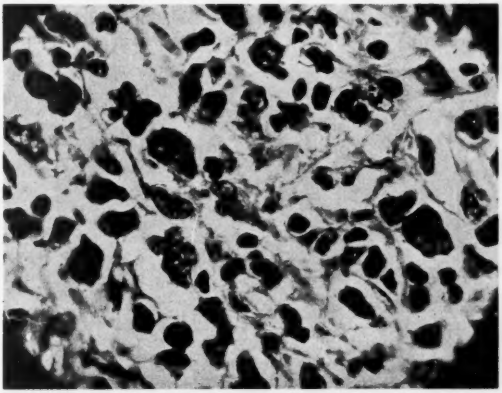

FIG. 1. Case 1. Microscopic section of spleen showing Sternberg-Reed giant cells (x850).

right portion of the pancreas and from the left kidney and adrenal gland showed no neoplasm. The diagnosis was sarcoma of the spleen with secondary involvement of the pancreas. Because of the Sternberg-Reed giant cells and the presence of connective tissue proliferation the tumor is now believed to be a Hodgkin's type of sarcoma. The histologic examination, together with the absence of involvement of any lymph nodes discoverable in the body except those immediately surrounding the portion of the pancreas involved by tumor, indicated that the neoplasm arose in the spleen.

Case 2. A woman, aged 64, was first seen on January 21, 1946, complaining of "sickening" pain in the left lower quadrant of two years' duration. For several months she had noticed increasing constipation and occasional bloody stools. Indigestion, nausea, and vomiting had been mild until three weeks prior to admission, when she began vomiting after almost every meal, sustaining sharp pain in the left side of the abdomen with each bowel movement and with micturition. X-ray films taken previously appeared to demonstrate neoplasm of the splenic flexure of the colon, although the previous fluoroscopic report states that an organic lesion of the sigmoid was suspected. The patient had lost 70 pounds in the past two years.

Physical examination revealed a rough, blowing systolic mitral murmur. Many small diffuse masses were present in each breast. An elongated mass adherent to surrounding deep tissues was felt in the left upper quadrant of the abdomen. A hard, tender mass, the size of

a baseball and not readily movable, could be palpated in this same region. Proctoscopic examination was negative for 25 cm.; x-ray examination of the chest negative; red blood cell count 5,040,000; hemoglobin, 13 Gm.; white blood cell count 14,250; 64 per cent neutrophils, 22 per cent lymphocytes, 3 per cent eosinophils, 9 per cent monocytes. Platelets and hemorrhagic studies, normal; investigation of blood chemistry, normal; Kahn and Wassermann tests, negative.

The preoperative diagnosis was neoplasm of the splenic flexure of the colon. At operation on January 30, 1946, the colon appeared normal, and no metastases were found in the liver. The spleen appeared about four times its normal size, with a rounded, elevated tumor mass involving the lower third and erasing the splenic notch. The top of this tumor had been mistaken for a baseball-sized mass in the colon. There were several enlarged pecan-sized lymph nodes at the hilus of the spleen. The spleen and several adjacent lymph nodes in the region of the splenic pedicle were removed. Nodules apparently involved by the neoplasm remained in the area of the pedicle and could not all be removed, but no retroperitoneal lymph node tumors were palpated. The gallbladder contained one stone the size of a plum.

There was no significant change in the blood picture following operation. A sternal puncture showed neither evidence of leukemia nor any malignancy. The patient had an uneventful recovery except for slight temperature elevation and mild nausea. The spleen weighed 806 Gm., measuring 22.8 x 12.3 x 8.7 cm. It was irregular in shape, nodular (fig. 2),

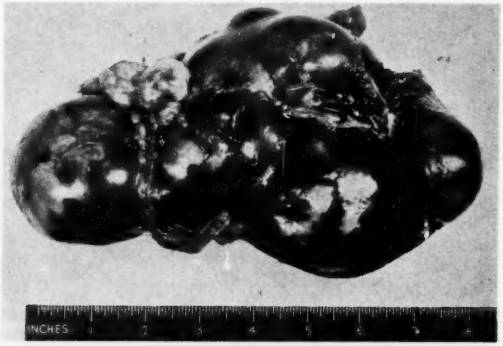

FIG. 2. Case 2. Gross specimen of spleen.

and numerous enlarged lymph nodes were massed together and attached to the hilus. The tumor portion of the spleen was firm with a very irregular, nodular-like pattern, yellowish-white in color, and bordered by the more normal appearing purplish-red tissue. The capsule was thickened. On cut section the tumor involved nine-tenths of the entire specimen and was not encapsulated. It showed numerous irregular, firm, glistening, moderately smooth, pink to yellowish-white, small and large nodules. Areas of necrosis contained a thick yellowish-green material. The tumor appeared to involve a portion of the capsule. The attached lymph nodes were greatly enlarged by a growth similar to that shown in the spleen. Veins in the hilus, especially in the attached fat, were thickened and enlarged. One nodule appeared to be nonencapsulated.

Histologic examination revealed the architectural structure of the spleen preserved in part in some areas, with the usual malpighian corpuscles and richly cellular pulp. The capsule was thick and contained many erythrocytes, lymphocytes, and large mononuclear cells. In general the lymph follicles were of moderate size, and the central arterioles showed thickening and hyalinization. In other regions the normal structure of the spleen was destroyed, and the cells were distinctly atypical. In addition to very cellular areas there were areas of fibrosis, and scattered cells contained granular brown pigment. The atypical cells varied considerably in size; some were multinucleated with several large irregularly shaped,

deeply chromatic nuclei, while others were mononuclear in type and variable in appearance, most of them having abundant cytoplasm and large vesicular nuclei. Abnormal nuclei and mitoses were present in moderate numbers.

Sections of lymph nodes showed one small node to be relatively normal except for a few atypical cells in the central portion; the larger lymph nodes showed much destruction of the architecture with considerable fibrosis and atypical cells similar to those in the spleen. Some had acidophilic cytoplasm, and most had vesicular nuclei. Multinucleated cells were present but not abundant. Abnormal nuclei and mitoses were present in moderate numbers. Other sections of both the spleen and lymph nodes stained for reticulum showed numerous coarse reticulin fibers and connective tissue separating groups of the atypical cells. A few fine reticulin fibers were also present between some of the cells. Diagnosis was leukoblastosis of the spleen and lymph nodes, too undifferentiated to distinguish it as an anaplastic reticular cell sarcoma or a Hodgkin's sarcoma. The Sternberg-Reed giant cells (fig. 3) supported the latter diagnosis. Absence of involvement of any other lymph nodes than those of the splenic pedicle in conjunction with the histologic findings indicated that the tumor was a primary neoplasm of the spleen. This sarcoma appeared to be a mixed type, having features of both a reticular cell sarcoma and a Hodgkin's sarcoma.

The patient was last seen April 24, 1946. She was feeling well except for occasional spells of nausea and vomiting. The constipation, lower abdominal pain, and melena were

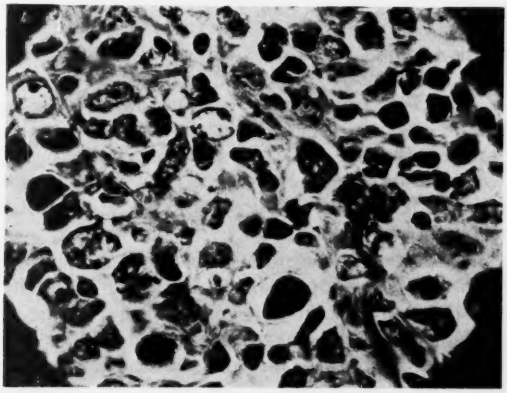

FIG. 3. Case 2. Microscopic section of spleen showing Sternberg-Reed giant cells (x850).

much improved. She may still suffer occasional nausea and vomiting because of the gallbladder condition discovered at operation. No definite mass could be palpated in the abdomen. The esophagus, stomach, and duodenum were shown normal by x-ray examination. Routine kidney-ureter-bladder flat plate roentgenogram showed only moderate hypertrophic changes in the lumbar vertebrae. Red blood cell count was 4,690,000 with 11.5 Gm. of hemoglobin, and white blood cell count was 11,500. Differential count showed 78 per cent neutrophils and 22 per cent lymphocytes. X-ray therapy was advised because of the enlarged lymph nodes at the splenic pedicle, not all of which could be removed.

Discussion

The presence of Sternberg-Reed type giant cells in a primary splenic sarcoma is rare and appeared to us of even greater interest than the finding of the rare condition of primary malignant disease of the spleen. It was the presence of these cells without the presence of plasma cells and eosinophils that led to

the difficulty in classification of these tumors and made the various classifications suggested in the literature appear inadequate. In reviewing 131 cases described in the literature, we are able to find 15 primary splenic malignant tumors where multinucleated cells are mentioned without presence of typical Hodgkin's granuloma, and we cannot determine from the descriptions how many of these are the Sternberg-Reed type giant cells. Menétrier[10] believed that the tumor which he named "splenoma" was derived from large mononuclear cells of the splenic cords. There were numerous giant cells containing inclusions of vacuoles. In areas not yet involved by the neoplasm an intense sclerosis, an endarteritis obliterans of the medium sized and smaller arteries, periarteritis, and disappearance or atrophy of the follicular elements were observed. A similar tumor was described by Foix and Roemmele,[11] who called it a nodular reticulo-splenoma and believed it to be derived from the reticular elements of the malpighian follicles. They believed a "round-cell sarcoma with giant cells" described by Simon (as cited by Smith and Rusk[12]) should also be classified splenoma. Duchemin[13] described another such tumor as a primary sarcoma of the spleen, but Menétrier considered it in the splenoma group. Langenstrasse and Neumann[14] described a primary endothelial sarcoma of the spleen, which classification Gerundo and Miller[15] later challenged, since they considered that the tumor arose from the reticulum without any endothelial origin or nature, as the cells had no angioblastic activities. They believed that this tumor fitted into Menétrier's splenoma group. Grayzel[16] described a reticular cell sarcoma of the spleen wherein an occasional tumor giant cell was seen. Smith and Rusk[12] described 9 endotheliomas with multinucleated giant cells. It is questionable whether these were of the Sternberg-Reed type.

The confusion of the various classifications as to the histologic diagnosis of primary malignancy in the spleen has been partially clarified by the adoption of the anatomic origin of the various neoplasms from splenic tissue. Bonney[8] classifies five tissues of origin: "connective tissue in the splenic capsule; reticular stroma of the spleen; lymphoid tissue surrounding the arterial vessels as an interrupted sheath, known as the splenic nodule or malpighian corpuscles; endothelial cells in the walls of the blood vessels; and reticulo-endothelial cells lining the splenic sinuses."

Hausmann and Gaarde[1] classify the tissue of the reticular stroma and malpighian corpuscles both under "lymphoid elements which give rise to lymphoma and lymphoblastoma," and subclassify these as follows:

A. Lymphosarcoma
   1. Large round cell (reticulum-cell type)
   2. Small round cell (lymphoblastic type)
   3. Giant lymph follicle hyperplastic

B. Hodgkin's granuloma

Neither of these classifications allows for adequate nomenclature for tumors of a mixed type. It is with this fact in mind that the hypothesis recently advanced by Herbut, Miller, and Erf[17] was noted with interest. They believe

that various combinations of Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma anywhere in the body can be explained only by considering the three diseases as arising from a common stem cell, the reticulum cell, and then differentiating in one direction or another according to the amount and type of stimulation. They present 6 cases which at one time were diagnosed as Hodgkin's disease and at another time as lymphosarcoma by biopsies and which at autopsy showed various combinations of Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma. They then describe the action of two substances, a myeloid stimulator (which can be separated into carbinols from the lipids of normal beef liver or the urine of patients with Hodgkin's disease or monocytic leukemia), and a lymphoid stimulator which can be separated into non-carbinols from the above materials. They further state that these substances appear to be mutually reciprocal when not in excess, "the myeloid stimulator causing the maturation of lymphoid cells, and the lymphoid stimulator causing the maturation of myeloid cells." Experiments on guinea pigs with these preparations are described. Herbut, Miller, and Erf suggest that lymphosarcoma might result from an excess locally of the lymphoid stimulator. They believe that reticulum cell sarcoma might result from an excess locally of both lymphoid and myeloid stimulators, each depressing the reciprocal maturating properties of the other so that stimulation of the common stem cell, the reticulum cell, might occur without maturation. Hodgkin's granuloma, according to these authors, might result from an excess of both stimulators but not in sufficient amount to preclude their reciprocal action and thus allow for a certain amount of maturation. The Sternberg-Reed tumor giant cell might then be derived from the common stem cell (reticulum cell), and the action of the stimulators on the blood-forming organs and connective tissue cells accounting for the proliferation, maturation, and destruction of many of the cellular elements of the blood and connective tissue that occur in Hodgkin's disease.

Final proof will probably depend on accomplishing the different procedure of tissue cell cultures and studying their response of the reticulum cell to these stimulator substances.

The derivation of these tumors from a common stem cell and their development by some variable combination of stimulators, together with the observation of a mixed cell type sarcoma and of varying cell types as different manifestations of apparently the same neoplastic disease, suggests to us the following modification of Class II of Hausmann and Gaarde's classification of primary neoplasms of the spleen, as a further clarification in classifying these tumors:

II. Lymphoblastomatous tumors arising from the common stem cell of the lymphoid and reticular elements, the reticulum cell.

- A. Lymphosarcoma
  1. Lymphoblastic (large round cell)
  2. Lymphocytic (small round cell)
  3. Giant follicular lymphoblastoma
- B. Reticular cell sarcoma

C. Hodgkin's granuloma and sarcoma

D. Mixed type sarcoma

1. Combinations of above cell types (mixed cell type)
2. Manifestations of different cell types in different areas of growth.

In this modification the large round cell rather than the small round cell is considered as the lymphoblastic type of lymphosarcoma. Hodgkin's sarcoma is included, in addition to Hodgkin's granuloma, as a more cellular, wildly growing, invasive tumor (such as case 1 here presented) than the granuloma. The reticulum cell sarcoma is considered in a distinct class derived from the common stem cell, therefore not belonging to the lymphosarcoma class. Case 2 is best classified as a mixed cell type sarcoma, having manifestations in a single tumor of a reticular cell sarcoma and a Hodgkin's sarcoma.

Many authors have discussed the advisability of splenectomy and the prognosis of primary neoplasm following this procedure. Whenever the tumor is operable without evident metastases other than local glandular involvement, it is apparently the procedure of choice. Our one patient operated on has progressed well, but it is yet too early to venture a favorable lengthy prognosis.

Summary

1. A case of primary splenic sarcoma of Hodgkin's type and a case of mixed cell type sarcoma with some manifestations of Hodgkin's sarcoma, also primary in the spleen, are reported, bringing the total number of reported primary malignancies of the spleen to 190.

2. Modern classification of primary splenic malignant tumors is discussed as to the problem arising from the 2 cases presented. A possible modification of the classification presented by Hausmann and Gaarde of the Mayo Clinic[1] is suggested.

The authors wish to express appreciation to Dr. John B. Hazard, Director of the Department of Pathology, Cleveland Clinic, for his interest in reviewing the pathologic slides, and his suggestions and comments. However, the opinions herein presented as to classification should not be assumed to be necessarily in agreement with his viewpoints.

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EOSINOPHILIC GRANULOMA

Report of a Case with Both Osseous and Cutaneous Lesions

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EOSINOPHILIC granuloma of bone was first recognized as a clinical entity during the past decade.[1,2,3] It is a destructive type of lesion involving usually the interior of the flat bones but occasionally the long bones. Not until a recent publication by Curtis and Cawley[4] have cutaneous manifestations been attributed to this condition, nor has the relationship between the osseous and skin lesions been established,[5] although such a relationship has been suggested.[6]

The case which we are reporting is of special interest because of the patient's age and the manifestation of both osseous and cutaneous lesions.

Case Report

A white baby girl, aged 12 weeks, was first seen at the Cleveland Clinic on March 4, 1946. The parents related that ten days previously they had noted that the child was protecting her right arm. On inspection of the shoulder a swelling was noted in the region of the scapula. The past history revealed that at birth delivery had been spontaneous and the weight was 8.5 pounds. Shortly afterward a papular rash was noted in scattered areas over the child's body. She had gained steadily until the onset of pain in the right shoulder.

On physical examination it was observed that movement of the right shoulder caused some pain. In the infraspinous portion of the scapula a fusiform thickening was palpated, which was smooth, slightly tender, and moved freely with the scapula. Over the chest, back, and buttocks there was a slightly scaly rash (fig. 1). These lesions were dull red in color and simulated an impetiginous eruption.

The laboratory examinations revealed a mild degree of secondary anemia. There was an elevation in the leukocyte count to 17,800, with the differential count showing 56 per cent polymorphonuclear cells, 34 per cent lymphocytes, 2 per cent eosinophils, and 8 per cent monocytes. The blood cholesterol level was within normal limits. The Wassermann and Kahn tests were negative.

Roentgenologic Examination. Roentgenograms were made of all the bones. The roentgenograms of the scapula (fig. 2a) showed expansion of the bone below the spine and evidence of osteolysis, but the cortex was not invaded. The left fifth rib contained a similar lesion, and the eleventh dorsal vertebra showed some narrowing and several small areas of osteolysis.

Pathologic Examination. A biopsy of the scapula, recommended at the time of examination, was done elsewhere and the tissue obtained was forwarded to us for examination.

The formalin-fixed specimens were prepared with hematoxylin and eosin stain. A section from a cutaneous lesion (fig. 3a) was also studied and revealed a localized area in the upper corium comprised of a dense, compact infiltration of lymphocytes, large mononuclear cells, and frequent eosinophils in small patches involving the superficial portion of the skin and extending downward to surround a hair follicle and several sweat glands. Over the entire extent of the lesion the epidermis was absent, being resumed with normal configuration at the immediate margin of the lesion.

Sections from a cancellous portion of the scapula (fig. 3b) revealed patches of callus

FIG. 2

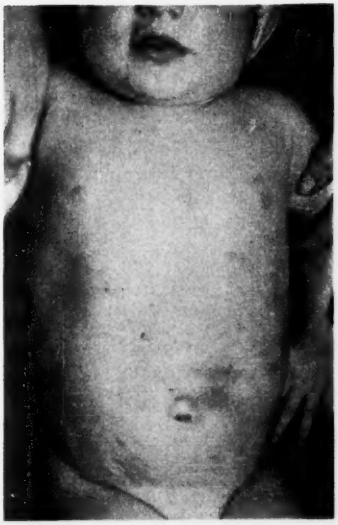
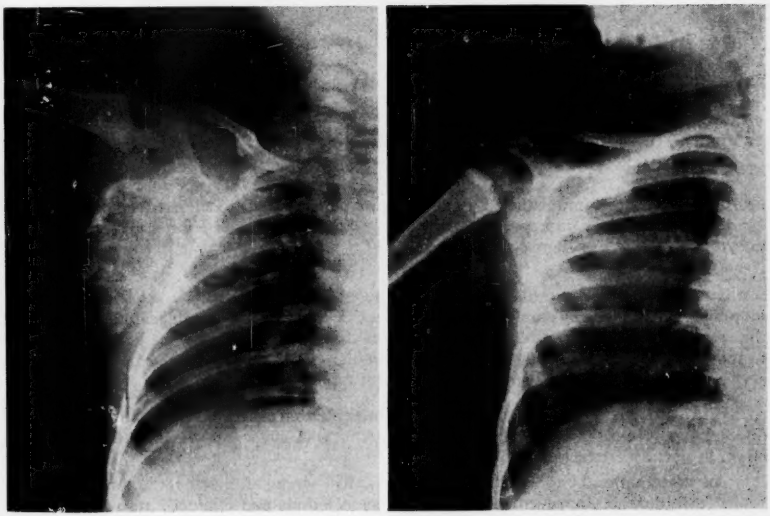
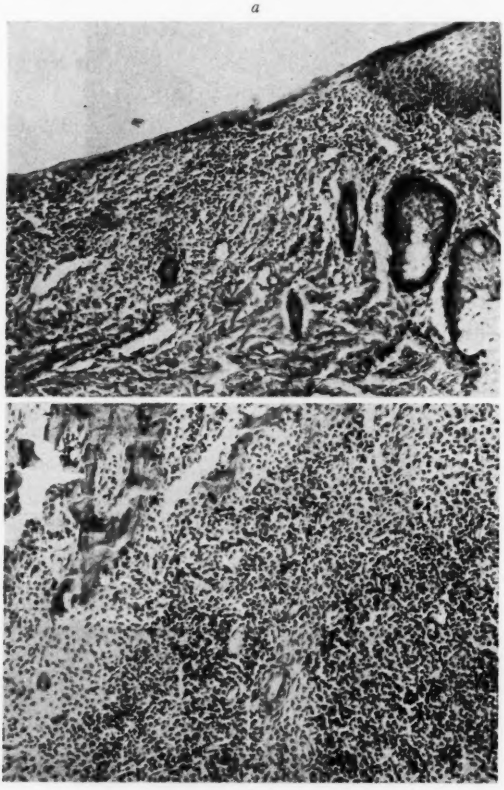


FIG. 1. Cutaneous lesions of the chest and abdomen.



a *b*

FIG. 2. (a) Initial appearance of scapular lesion. (b) Scapular lesion sixteen months after treatment.



a

b

FIG. 3. Lymphocytic infiltration of upper corium, patches of histiocytes, scattered eosinophils. Epidermis thinned or absent over lesion (x50). (b) Large foci of eosinophils, zones of histiocytes including one giant cell in bone (x50).

contiguous to cellular granulation tissue composed of many histiocytic cells, masses of eosinophils, and occasional patches of lymphocytes. Many small multinucleated giant cells of the osteoclastic type were present in the cellular tissue adjoining the bone and also adjacent to the callus. The surrounding dense connective tissue was also infiltrated by patches of the above-mentioned cells. One small area of infarct type necrosis was noted.

Clinical Course. Radiation therapy was instituted on April 23, 1946, and was given in divided exposures over a period of three days. A total of 200 r was given to the scapula and eleventh dorsal vertebra and 150 r to the rib.

An examination of the patient on May 27, five weeks after the radiation therapy, revealed considerable improvement in the cutaneous lesions and clinical improvement in use of the arm but no reduction in size of the scapula.

A roentgenologic examination made on August 20, four months after the radiation therapy, revealed marked improvement, and the child had no discomfort in her arm.

The child was last seen on August 19, 1947. Her development had been normal and at that time she was in excellent health. The skin lesions were healed with small areas of scarring. There was a scar over the lower portion of the scapula where the biopsy had been made, but there was no evidence of abnormality in the contour of the scapula or of dysfunction in the arm. A roentgenogram (fig. 2b) made at that time showed that the osseous lesions had completely healed and the bones had assumed their normal texture and contour.

Summary

The case of eosinophilic granuloma of the bone discussed is believed to represent the youngest patient reported in the literature. The patient exhibited skin lesions which are probably cutaneous manifestations of this disease.

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CARCINOMA OF THE PANCREAS

With Special Reference to the Body and Tail

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CARCINOMA of the pancreas does not occur as frequently as do other malignant tumors of the gastrointestinal tract. Lahey[1] estimates the incidence between 1 and 2 per cent of all malignant tumors. Between 1928 and 1930, deaths due to carcinoma of the pancreas represented 4.8 per cent of all cancer deaths in the hospitals of the state of Massachusetts (Bigelow[2]).

The original description of carcinoma of the head of the pancreas by Bard and Pic[3] in 1888 was readily accepted, and the classical "progressive painless jaundice" has been associated ever since with the diagnosis. However, this description does not include all the types of carcinoma of the pancreas; Chauffard[4] in 1908 described the clinical entity, and his description of the pain still applies.

The clinical manifestations of carcinoma of the pancreas, with the exception of a palpable tumor mass, result from changes in the neighboring organs, such as the common duct, duodenum, and stomach. The whole pancreas forms one physiologic entity. Direct symptoms resulting from possible alteration of the physiology of the pancreas (hyperglycemia) are minimal, as has been recognized by most writers.

Ransom[5] in 1935 and Duff[6] in 1939 presented excellent reviews of the subject, considering carcinoma of the body and tail as different clinical entities from carcinoma of the head. Ransom reviewed 16 proved cases of carcinoma of the body and tail of the pancreas, while Duff reported 19 cases in which only the body and tail were involved and 3 cases in which the whole gland was involved. All of these cases were proved at autopsy.

The comparative incidence of carcinoma of the head and of the body is difficult to establish. In the cases reported in the literature and those in which there has been no operation or autopsy, the incidence of carcinoma of the head is higher, whereas the incidence of carcinoma of the body and tail is higher in those cases having had operation or autopsy. The reason for this discrepancy is that in most cases of carcinoma of the head the diagnosis is based on clinical evidence alone, and most of these patients die at home. On the other hand, carcinoma of the body and tail is obscure and difficult to diagnose clinically, and for that reason most patients have had an exploratory laparotomy, or an autopsy has been performed after death to clarify the diagnosis.

Leven[7], in his two series, one from autopsy cases and one from hospital cases, shows this discrepancy: of the hospital cases 22 were diagnosed as carcinoma of the head, 2 of the body or tail, and 6 of the whole pancreas. In his

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autopsy series of 97 cases, 60 were diagnosed as carcinoma of the head, 19 of the body or tail, and 18 of the whole pancreas. As can be seen in the hospital series, the incidence of carcinoma of the body is one-tenth that of carcinoma of the head, and in the autopsy series the incidence is one-third.

In our own series of 31 cases 13 were considered carcinoma of the head, 12 carcinoma of the body and tail, 1 carcinoma of the head and body, 2 carcinoma of the entire organ, and in 3 cases the exact location of the lesion is not mentioned in the records. All of these patients were operated upon or had an autopsy.

Age and Sex. In our series of 12 proved cases of carcinoma of the body and tail the youngest patient was 42 years old and the oldest 78. In our series of carcinoma of the head the youngest patient was 37. Carcinoma of the pancreas is a disease seldom present before the fourth decade of life. Of the patients with carcinoma of the body and tail 7 were male and 5 were female. These figures agree with those reported by other authors (Ransom, Duff, Leven).

Pain. The outstanding clinical symptom in our cases was severe epigastric pain radiating to the back, worse at night, and not relieved by food or alkalies. The pain seemed to bear no relation to meals. In some cases the pain was referred to the back, and in 1 it was the only symptom and so severe in nature that a cordotomy was performed. It was not until postmortem examination a short time later that carcinoma involving the entire pancreas was found. In most of our cases the pain was described as severe in nature but was also described as dull, aching, or boring. There was a previous history of gastrointestinal symptoms in a few cases but in the majority pain was the first and only symptom.

The explanation for the severity of the pain in carcinoma of the body and tail of the pancreas was pointed out by Chauffard in his original communication and verified by Duff. The cancer cells extend along the nerve sheaths of the solar plexus, and when the patient lies on his back the protrusion of the spine and the compression caused by the gland exacerbates the pain. Thus many patients obtain relief from the night pain by sitting up in bed or flexing their thighs over the abdomen.

Weight. The other outstanding symptom in our series was marked loss of weight, the average loss being 20 pounds in four or five months. This is comparable with the series reported by Ransom and Duff. There seems to be no difference in the weight loss in the cases of carcinoma of the head and in those of carcinoma of the body and tail. Weight loss was not the chief complaint of our patients, as in Ransom's series, but it is an outstanding symptom. This and pain, we believe, are the cardinal symptoms of carcinoma of the body and tail of the pancreas.

Constipation. Constipation is frequent and becomes more pronounced as the disease progresses. In our experience this was a misleading symptom, and in several cases a preliminary clinical diagnosis of carcinoma of the colon was made.

Jaundice. In general, jaundice in carcinoma of the head of the pancreas follows the classical description of Bard and Pic except that it is not always

painless. Of our 13 patients 12 had jaundice. Of our 12 patients with carcinoma of the body and tail, none had jaundice.

Palpable abdominal mass. Only 3 of our 12 patients with carcinoma of the head had a palpable abdominal mass. Of our 12 cases of carcinoma of the body and tail an abdominal mass was palpated in 5. The size of this mass varied between that of a walnut and that of a grapefruit. The location of the tumor mass was always epigastric, and it was described as hard and not tender. A palpable abdominal mass was present in 1 of the 3 cases in which the exact location of the carcinoma was not established. In 2 cases involving the whole gland, 1 had a palpable abdominal mass.

We can consider that in half of our cases of carcinoma of the body and tail there was a palpable tumor mass. These findings are similar to the series reported by Ransom (8 cases out of 16). In 2 of our cases the mass was described as moving with respiration, and a preliminary diagnosis of carcinoma of the transverse colon was made.

Gastrointestinal bleeding. Only 1 patient with carcinoma of the body and tail had hematemesis; no ulceration was palpated either in the stomach or the duodenum at the time of an exploratory laparotomy. In 2 cases occult blood was present in the stools; in 1 of these cases a gastric crater was suggested at the time of the roentgenologic examination, but at the time of the operation the stomach was considered normal by palpation. There were no roentgenologic or surgical findings to account for the bleeding in the other case.

Roentgenologic Findings

As the pancreas is a radiolucent organ and of the same density as the neighboring structures, it is impossible to obtain any conclusive information from the plain roentgenogram.

In only 1 of our cases was there a calcified cyst-like structure present in the right upper quadrant. This was a heavily vascularized carcinoma of the head of the pancreas. Originally this calcification was interpreted as a renal cyst, and the patient was operated upon under this diagnosis.

Attempts have been made by many investigators to achieve better visualization of the pancreas during roentgenologic examination. Pneumoperitoneum has been advocated but has not been widely popularized because of the difficult technic. We have had no experience with this method.

So far, no contrast medium is available for visualization of the pancreas. In general the radiologic study of the pancreas must be made by indirect means based on the anatomic relationship of this organ to other structures.

Special technics have been described for the diagnosis of pancreatic tumors. Engel and Lysholm[8] advocate the use of a gas-producing mixture which will distend the stomach, thereby causing the pancreas to impress its shadow on the gas-filled organ. Immediately after this a lateral abdominal decubitus film is exposed. Lysholm established the normal size of the pancreas as the width of a vertebral body.

Hershenson[9] has described a technic by which he was able to diagnose a case of carcinoma of the body and tail of the pancreas. During the gastric

examination the patient is placed prone under fluoroscopic control on a tilting table. This is tilted down between 20 and 45 degrees. The tumor mass compressed between the abdominal wall, the stomach, and the spine produces a filling defect along the body of the stomach; this defect appears between the 20 and 45-degree angle.

In our own series no specialized technic was employed; our patients had a gastrointestinal examination and were examined in upright, supine, and prone positions.

There are two signs which have been described as characteristic of pancreatic neoplasms. The first is the fan-like widening of the duodenal loop; this sign is not pathognomonic of carcinoma of the pancreas but can be found in all types of pancreatic tumors. When the duodenum exhibits distorted folds and ragged edges a carcinoma of the pancreas is suggested. A smooth appearance of the duodenum with widening of the long fold but without distortion of the folds is often present in pancreatic cysts.

The second sign is Frostberg's[10] reverse three (Ɛ), which has been described as characteristic of carcinoma of the head of the pancreas and of the ampulla of Vater. We believe this sign to be present more commonly in the latter instance. In none of our series of carcinoma of the head of the pancreas were we able to identify a Frostberg's sign which fitted the description given by the author.

An evaluation of the roentgenologic findings in carcinoma of the pancreas in our series of cases is as follows:

Of 13 cases of carcinoma of the head 8 had examinations of the stomach and colon. One showed deformity of the duodenal bulb which was interpreted in the original examination as "ulcer deformity without crater." The second case showed a deformed duodenal bulb but due to the smoothness of this deformity had been interpreted as the result of extrinsic pressure. The third showed a compression deformity of the distal antrum, along the lesser curvature, and some extrinsic pressure of the duodenal bulb. This case also had an atypical, wide, fan-like duodenal loop. A fourth case had evidence of extrinsic pressure in the antrum along the lesser curvature.

In a fifth case in which a calcified cyst-like structure was present in the right upper quadrant, the stomach and duodenum were normal, but the examination of the colon revealed a downward displacement of the hepatic flexure. This has been the only case in which we have been able to identify any evidence of displacement of the transverse colon. Also in this case there was a nonfunctioning right kidney, demonstrated by an intravenous urogram. This patient was explored and a large, fungating, heavily vascularized carcinoma of the head of the pancreas invading the right renal region was found.

In 3 cases a normal stomach, duodenum, and colon were found. Gallbladder examination was of no particular interest except that in all the patients who had jaundice there was a nonfunctioning gallbladder.

Of our 13 cases of carcinoma of the body and tail 10 patients had barium studies of the stomach and colon, 1 had a colon examination only, and 1 had a gallbladder examination. Of the 10 patients that were examined completely,

5 failed to show any abnormality either at the time of the original examination or in the review of the roentgenograms. One patient had a typical ulcer crater along the lesser curvature on the posterior wall of the stomach. This ulcer crater was thought to be present in three consecutive roentgenologic examinations but was not demonstrated at gastroscopic study. Occult blood was present in the stools. This patient had severe epigastric pain radiating to the lumbar spine which failed to improve under strict ulcer medical management. An exploratory laparotomy was performed and a white, fixed carcinoma of the body of the pancreas, the size of an orange, was found. The stomach and duodenum were normal to palpation. In another case x-ray examination showed a small tongue-like projection of barium along the lesser curvature of the gastric antrum. This patient had a palpable abdominal mass; there was no evidence of extrinsic pressure in the roentgenograms. An exploratory laparotomy revealed a carcinoma of the body of the pancreas the size of a grapefruit. The stomach and duodenum were normal to palpation. A third patient had roentgenologic evidence of extrinsic pressure along the lesser curvature of the stomach. This patient also had a palpable abdominal mass. In 2 cases pressure deformity suggesting an organic lesion in the third portion of the duodenum was demonstrated on the roentgenograms. In another case a partial obstructing lesion was present just proximal to the ligament of Treitz. Roentgenograms demonstrated gastric retention and considerable dilation of the duodenum proximal to the obstruction. An exploratory laparotomy revealed a carcinoma of the body and tail of the pancreas the size of a grapefruit compressing the third portion of the duodenum.

In 1 case a broadening of the third portion of the duodenum with normal mucosal folds was found. This was interpreted as extrinsic pressure deformity. At the time of surgical exploration a carcinoma of the body and tail of the pancreas compressing the third portion of the duodenum was found.

In none of our cases of carcinoma of the body and tail was evidence of compression or displacement of the colon found.

From this study it is apparent that abnormal roentgenologic findings were present in 10 of the 18 patients with carcinoma of the pancreas in whom x-ray studies of the gastrointestinal tract were made. Pressure deformity of the duodenum or stomach is the most characteristic roentgenologic finding. The deformity may occasionally produce changes suggesting gastric or duodenal ulcer. This latter finding may be misleading and cause delay in performing an exploratory laparotomy. Roentgenologic findings are not pathognomonic for carcinoma of the pancreas, but the secondary signs described are definitely contributory to the diagnosis in a large percentage of the cases.

Conclusions

1. In carcinoma of the body and tail of the pancreas the common and most important symptoms are (1) pain with characteristic radiation to the back and (2) severe loss of weight. Jaundice is a prominent symptom only in carcinoma of the head of the pancreas.

2. The roentgenologic findings have been shown to be contributory in establishing a diagnosis in a large percentage of the cases. The efforts of the roentgenologist should be directed toward detecting any evidence of extrinsic pressure either in the stomach or the duodenum.

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BONE MARROW STUDIES IN HODGKIN'S DISEASE

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Osseous involvement in Hodgkin's disease has been reported in numerous papers, with a varying percentage of cases showing typical bone lesions either by roentgenologic study or by microscopic examination of the pathologic tissue. In 172 cases studied, Craver and Copeland[1] found bone involvement in 15.7 per cent. Goldman[2] reported roentgenologic evidence of disturbances of the osseous system in 6.6 per cent of 212 cases. Lymphogranulomatous foci of the bone marrow were found in 11 of 14 cases of Hodgkin's disease examined by Steiner,[3] and in 7 of the 11 cases examined the sternal marrow was involved. It has been shown repeatedly that the bones containing active hematopoietic tissue, such as the vertebrae, sternum, pelvis, skull, and ribs, are most often affected.

Morrison and Samwick[4] reported bone marrow aspirations to be a diagnostic aid in 8 cases of Hodgkin's disease in which clinical signs and symptoms and routine blood examinations failed to be of assistance. They noted that the red cell mechanism showed slightly increased activity but that, on the other hand, there was an increase in reticulum cells and a moderate eosinophilia and increase in megakaryocytes. Varadi[5] was able to make the diagnosis of Hodgkin's disease by sternal puncture in 1 case. The aspirated material contained a mixture of blood, fat droplets, lymphocytes, and large cells with enormous nuclei, containing nucleoli, which were considered to be Sternberg cells. In the same case Sternberg cells were found on puncture of a lymph gland and also on histologic examination. X-ray examination of the sternum revealed no pathologic finding except for slight rarefaction.

Paraf *et al.*[6] reported a case of Hodgkin's disease with clinical and roentgenologic evidence of involvement of the sternum which could not be diagnosed by sternal puncture, as the repeated aspirations revealed hypoplasia of the bone marrow. In this case, Sternberg cells were abundant in biopsy studies of an involved lymph gland and also of cutaneous nodules.

Materials and Methods

In this paper are recorded the observations made at Cleveland Clinic on the bone marrow smears of 8 patients with Hodgkin's disease. The diagnosis was confirmed in all cases by biopsy of lymph nodes or by autopsy. All of these patients either had enlarged lymph nodes at the time of examination or gave a history of glandular enlargement during the course of their illness. Three patients had hepatomegaly and 4 had splenomegaly; 1 patient had both.

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The temperatures of these patients varied from 99 to 104 F. at the time of their initial examinations. All gave a history of weight loss. One patient had regained and maintained his weight after having received x-ray therapy one year previously. Roentgenograms of the chest were made on all patients, and evidence of mediastinal disease or hilar gland enlargement was noted in four instances. Four patients had received x-ray therapy prior to the sternal punctures. The Wassermann and Kahn tests were negative in all patients. The peripheral blood picture varied in different patients but in all cases was consistent with the diagnosis of Hodgkin's disease.

The marrow preparations were made on coverslips from material aspirated from the sternal marrow. A minimal amount of marrow was aspirated in order to avoid dilution with peripheral blood. The smears were stained with Wright's stain. In making the differential count 200 or more cells were examined.

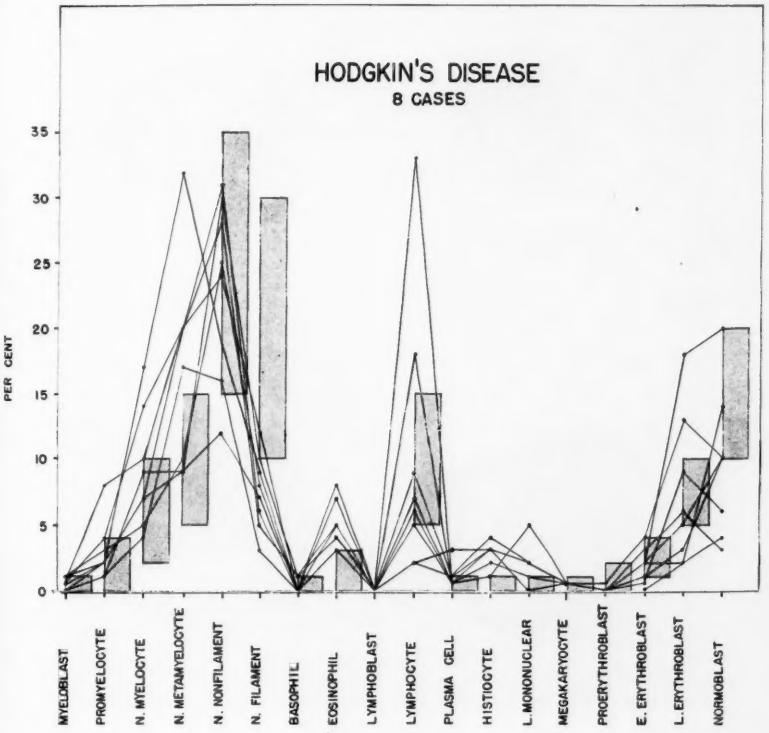

FIG. 1. Cell distribution in bone marrow smears. Normal range of variation represented by shaded areas.

The megakaryocyte counts were made, noting the number per 10,000 consecutive nucleated cells. The megakaryocytes were classified as megakaryoblasts, immature, intermediate, and mature megakaryocytes, or a naked nuclei. Twenty-five or more megakaryocytes were examined in each case.

Observation

The distribution of the various cell types in the 8 cases of Hodgkin's disease is graphically represented in fig. 1.

The sternal marrow was found to be cellular in 7 cases and hypoplastic in 1. This patient had received a large amount of x-ray therapy. There was a tendency toward a shift to the left in the myeloid series. There was an increase in eosinophils in 5 cases, and the level of these cells was at the upper limit of

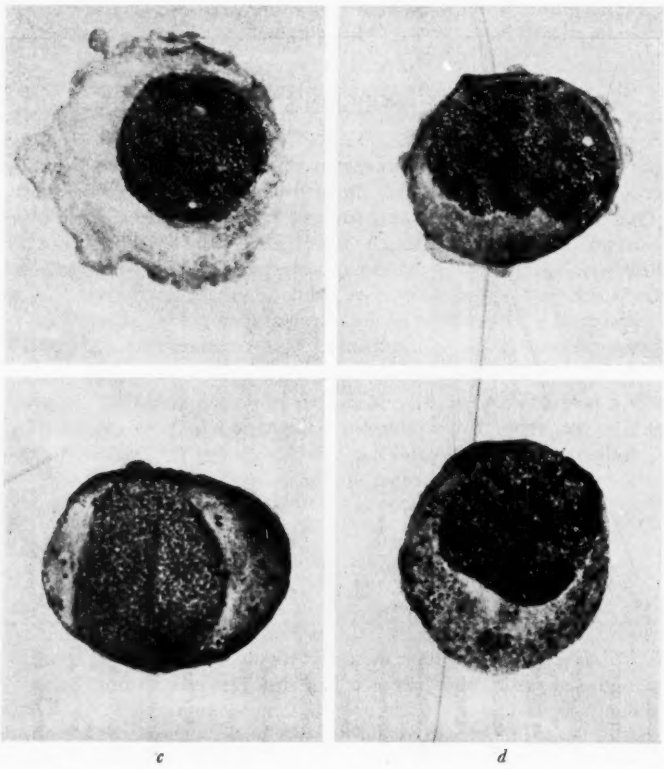

FIG. 2. Cell types found in the bone marrow, Hodgkin's disease. (a) Undifferentiated reticulum cell. (b) Early cell with indented nucleus and pseudopods. (c, d) Large atypical granular mononuclears.

normal in the other 3 cases. Basophils were rarely found. Lymphocytes were increased in 2 cases. Plasma cells constituted 3 per cent of the nucleated cells in 1 case but in the other 7 cases were 1 per cent or less. The mononuclear count varied from 1 to 5 per cent. Reticulum cells were slightly increased in all cases, the percentage varying from 1 to 4.

Atypical cells which were morphologically on the border line between reticulum cells, large mononuclears, and promyelocytes were demonstrable in all smears but usually constituted less than 1 per cent of the nucleated cells. These atypical cells were large, having a diameter greater than the usual myeloblast or promyelocyte. The shape of the nucleus varied from round to lobulated. The majority of cells were indented and had brain-like convolutions or folds. In most of the cells there was a well-defined, delicate chromatin

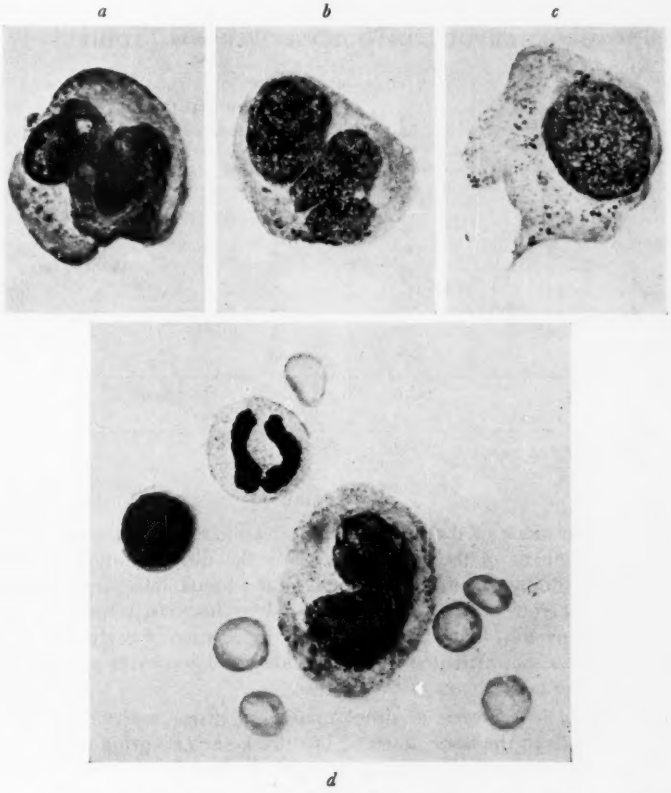

FIG. 3. Cell type found in bone marrow, Hodgkin's disease. (a, b) Atypical large mononuclears. (c) Histiocyte. (d) Atypical large mononuclear, showing size in relation to red cells, lymphocyte, and filamented neutrophil.

structure and nucleoli. In later and partially degenerate forms pyknosis was demonstrable. Although the nucleus was large the cytoplasm was also ample. The granules varied in size and distribution (figs. 2 and 3). Vacuoles and small multiple or large pseudopods were sometimes observed. Transition forms between the abnormal cells and undifferentiated reticulum cells, histiocytes, and mononuclears can readily be demonstrated.

Erythroid elements were within normal limits with the exception of 1 case in which they were present in decreased numbers. Megakaryocytes were considered to be moderately increased in the 7 cases counted (table). The megakaryocytes tended to be mature except in the case with purpura. Platelets appeared to be present in normal numbers, but in the case of purpura they were markedly decreased.

TABLE

MEGAKARYOCYTES IN BONE MARROW STUDIES

Case	Megakaryocytes per 10,000 nucleated cells	Differential Count			
		Immature	Intermediate	Mature	Naked Nuclei
1	29	4	28	52	16
2	23	0	8	8	84
3	18	0	16	76	8
4	14	0	5	65	30
5	35	4	12	84	0
6	28	0	5	75	20
7*	32	20	68	12	0
Normal	4–20	0–10	9–36	50–80	0–26

* *This patient also had purpura.*

Discussion

The greatest value of the bone marrow examination in diseases characterized by enlargement of the lymph glands is the differentiation of leukemia from other conditions. In monocytic or lymphoid leukemia there is a replacement of the marrow cells by monocytes or lymphocytes, some of which are immature. In myeloid leukemia there is predominance of early myeloid cells. In the leukemias the nucleated red cells and megakaryocytes are significantly decreased in the later stages of the disease.

Occasionally in sarcoma or other malignant diseases one may find diagnostic tumor cells in the bone marrow, but this is the exception rather than the rule. The bone marrow examination is of little value in differentiating Hodgkin's disease from tuberculosis and other chronic inflammatory diseases, for in these conditions there is also a hyperplastic marrow with a pleomorphic cellular reaction and atypical reticulum cells.

Summary

The bone marrow smears from 8 patients with Hodgkin's disease examined at Cleveland Clinic revealed fairly consistent abnormalities which, while not diagnostic, are considered to be of value in differential diagnosis and of confirmatory value in suspicious cases. The marrow is usually cellular and the myeloiderythroid ratio essentially normal. There is slight myeloid immaturity. The eosinophils, mononuclears, histiocytes, and sometimes the lymphocytes are slightly increased. Large, atypical cells characterized by folded, indented, or lobulated nuclei, early nuclear structure, and variable granularity are demonstrable. Megakaryocytes are present in increased numbers and are of mature variety.

References

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday, March 18, 19, and 20, 1948

DISEASES OF VEINS, ARTERIES, AND LYMPH VESSELS

Tentative Program

Thursday, March 18, 1948

8:00-9:00 a.m.	Registration	
9:00 a.m.	Mechanisms of Peripheral Circulation	A. C. CORCORAN, M.D.
9:30 a.m.	Normal and Collateral Circulation in the Extremities—Movies, Slides	D. P. QUIRING, M.D.
10:15 a.m.	Physical Examination and Special Technics—Demonstration	F. A. LEFEVRE, M.D.
11:00 a.m.	Angiography	C. R. HUGHES, M.D.
11:30 a.m.	Pathogenesis of Arteriosclerosis	I. H. PAGE, M.D.
1:30 p.m.	Thromboangiitis and Arteriosclerosis Obliterans Differential Diagnosis	EDGAR V. ALLEN, M.D.
2:15 p.m.	Thrombophlebitis and Varicose Veins	F. A. LEFEVRE, M.D.
3:00 p.m.	Psychosomatic Aspects of Vascular Disease	G. H. WILLIAMS, JR., M.D.
3:30 p.m.	Differential Diagnosis of Cutaneous Lesions on the Leg	E. W. NETHERTON, M.D.
4:00 p.m.	Aortic and Peripheral Aneurysms	A. C. ERNSTENE, M.D.
8:00 p.m.	Anticoagulants	EDGAR V. ALLEN, M.D.

Friday, March 19, 1948

8:30 a.m.	Periarthritis of Shoulder with Vascular Disease of Hand	R. L. HADEN, M.D.
9:00 a.m.	Raynaud's Disease and Other Diseases of Peripheral Circulation	R. D. TAYLOR, M.D.
10:00 a.m.	Demonstration of Patients	DRS. ALLEN, ERNSTENE, and LEFEVRE
1:30 p.m.	Arteriovenous Fistulas	EDGAR V. ALLEN, M.D.
2:15 p.m.	Pathologic Findings of Blood Vessel Disease	J. B. HAZARD, M.D.
3:00 p.m.	Panel Discussion—Questions and Answers	
	DRS. DETAKATS, ALLEN, LEFEVRE, and PAGE with DR. JORDAN as moderator	
8:00 p.m.	Surgical Treatment of Arterial Disease	GEZA DETAKATS, M.D.

Saturday, March 20, 1948

8:30 a.m.	Medical Management of Arterial and Venous Disease	F. A. LEFEVRE, M.D.
9:15 a.m.	Surgical Management of Varicose Veins	GEZA DETAKATS, M.D.
10:00 a.m.	Anesthetic Agents and Methods in Vascular Disease	D. E. HALE, M.D.
10:30 a.m.	Amputations in Arterial and Venous Disease	J. A. DICKSON, M.D.
11:00 a.m.	Surgery upon Sympathetic Nervous System as Treatment for Vascular Disease	W. JAMES GARDNER, M.D.
11:30 a.m.	Surgical Treatment of Aneurysms	GEORGE CRILE, JR., M.D.

Meals can be obtained in the cafeteria of the Cleveland Clinic Hospital.

REGISTRATION BLANK

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE ....., 1948
Cleveland Clinic Building
2020 East Ninety-third Street
Cleveland 6, Ohio
Gentlemen:

Please register me for the course on "Diseases of Veins, Arteries, and Lymph Vessels" which is to be given March 18, 19, and 20, 1948.

I am sending check for $5.00, and the remainder of the fee, $5.00, will be paid on Registration, March 18.

NOTE: Checks should be made payable to the Frank E. Bunts Institute. Mail registration blank and check to Dr. Edwin P. Jordan, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Name .....

Address .....

Medical School and
date of graduation .....

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be adequately accommodated.

APPOINTMENTS

Clarence M. Taylor has recently been made executive director of the Cleveland Clinic. The Cleveland Clinic has been without an operating head since the death of Mr. Edward C. Daoust in an airplane accident last summer. Mr. Taylor has been associated with the Lincoln Electric Company of Cleveland since his graduation from Western Reserve University in 1916 with the exception of three years as pilot in the Army Air Corps in World War I. After serving in various capacities, he was appointed executive vice-president of the Lincoln Electric Company in 1946.

Mr. Taylor was educated at Shaw High School and Western Reserve University, where he was captain of the 1915 Ohio Conference Champions. He is a trustee of Fenn College, Western Reserve University, and the McGregor Home.

Dr. Edwin P. Jordan has been appointed director of Medical Education for the Frank E. Bunts Educational Institute. Formerly of Chicago, Dr. Jordan was for ten years associate editor of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION and editor of the STANDARD NOMENCLATURE OF DISEASE AND OPERATIONS. He graduated from the University of Chicago in 1923 and Rush Medical College in 1927.

BUNTS LECTURES

The Frank E. Bunts Educational Institute has scheduled the following Bunts lectures in the coming months. These lectures will be held in the Founders and Staff Room of the Cleveland Clinic at 8 P.M. Visitors are cordially invited.

January 14, 1948 —Dr. Jean Oliver
The Nephrons in Health and Disease

February 11, 1948—Dr. Edward D. Churchill
Current Problems in Pulmonary Surgery

April 14, 1948 —Dr. Paul Klemperer
Changes of the Collagenous Tissues in Disease